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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/466,698	06/06/95	SANSONETTI	P 2356.0043-02

EXAMINER
CAPUTA, A

ART UNIT	PAPER NUMBER
1806	

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FINNEGAN HENDERSON FARABOW
GARRETT & DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/466,698	Applicant(s) Sansonetti et al.
	Examiner Anthony C. Caputa	Group Art Unit 1806

☒ Responsive to communication(s) filed on *Mar 22, 1996* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-10 and 13* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-10 and 13* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Serial Number: 08/466,698
Art Unit: 1806

Part III DETAILED ACTION

1. Applicants' amendment and declaration were received 3/22/96 and entered as Paper nos. 7 and 8, respectively. Claims 10, 11 have been cancelled. Claims 1-10, and 13 are pending.

Specification

2. The prior objection to the title is maintained as set forth in the last Office Action.

Applicants' amendment is not sufficient to overcome the objection as set forth in the last Office Action since a title is required that is clearly indicative of the invention to which the claims are directed. It is suggested by the Examiner applicants' amend the title as follows:

"Methods for Producing Transformed Shigella that Cannot Produce Toxins"

to obviate the objection to the title.

3. The prior objection to the use of trademarks is withdrawn in view of applicants' amendment.

4. Applicants' acknowledgement that references cited in the specification but not cited in compliance with 37 CFR 1.98 have not been considered is noted.

Claim Rejections - 35 USC § 112 2nd paragraph

5. The prior rejection of claims 1-10 under 35 U.S.C. § 112, second paragraph, for use of the term "characterized" is withdrawn in view of applicants' amendment.

6. The prior rejection of claims 1-10 under 35 U.S.C. § 112, second paragraph, for the recitation of "substantially" and "substantial" is maintained.

As set forth previously, "It is not clear what constitutes as "substantially" or "substantial"? Applicants argue the terms "substantial" and "substantially" have been accepted by the courts. Applicants are noted. However, since the terms "substantially" or "substantial" are not specifically defined in the specification with regard to a definite level, degree, or range the rejection is maintained. See *In re Nehrenberg (CCPA) 126 USPQ 383.*

Claim Rejections - 35 USC § 112/1st paragraph

7. The prior rejection of claims 1-10, and 13 under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure of how to use the claimed modified Shigella as a vaccine is withdrawn upon further consideration of the Examiner upon review of the file of the parent application 08/118,100 (see particularly Paper No. 20 of the parent application 08/118,100).

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one skilled in the art how to make and/or use the claimed invention, i.e. failing to provide an enabling disclosure.

As set previously, it is apparent that numerous modified Shigella are required to practice the claimed invention. That is, one skilled in the art can not make the claimed microorganisms or vaccines without the Shigella species which

contain the claimed inactivated genes. Accordingly as a required element, the modified Shigella must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available the enable requirements of 35 U.S.C. § 112, first paragraph may be satisfied by the deposit of the claimed microorganisms and limiting the claims to the deposited mutants. See 37 C.F.R 1.802.

In the instant case the construction of claimed Shigella mutants requires knowledge of the nucleotide sequence of said genes, which regions are responsible for biological activity, and the number of nucleotides which must be deleted or inserted. Due to the limited teaching of the specification and the unpredictable nature of which mutations are useful one skilled in the art can not practice the invention as claimed absent undue experimentation. In view of the foregoing the only means by which applicants can provide an enabling disclosure for the Shigella mutants is by depositing said mutants and limiting the claims to the deposited mutants.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required. As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits

comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;
2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if the test is not done by the depository; and
7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the Shigella mutants described in the specification as filed is the same as that deposited in the depository. Corroboration

may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

Applicants urge that the specification provides sufficient teachings for one skilled in the art to practice the claimed invention. Applicants state that the specification teach of methods of modification to employ in order to inactivate the genes. These arguments are not considered persuasive. The decisional law has held the mere recitation in the specification of a broad concept does not necessarily provide a sufficient basis for broadly claiming it (i.e. transposon mutagenesis). See Ex parte Gardner 157 USPQ 162 (Bd. Pat. Appls and Interf. 1967), In re Cavallilo, 127 USPQ 202 (CCPA 1969). The fact that the terms in a claim are the same as those in the specification does not prevent the claims from being rejected as unduly broad if they define subject matter not define subject matter not described to be the actual invention by means of adequate representative samples. See in re Lund, 153 USPQ 625 (CCPA 1967). In the instant case the construction of claimed Shigella mutants requires knowledge of the nucleotide sequence of said genes (iscA, virG, aerobactin, enterochelin), which regions are responsible for biological activity, and the number of nucleotides which must be deleted or inserted. For Support of the Examiner's position is found in applicants own response that Mills et al. does not characterize the location of such deletions (see page 10 of Paper No. 7). Due to the limited teaching of the specification and the unpredictable nature of which mutations are useful one skilled in the art can not practice the invention as claimed absent undue experimentation. In view of the foregoing the only means by which applicants can provide an enabling

disclosure for the Shigella mutants is by depositing said mutants and limiting the claims to the deposited mutants.

The declarations under 37 C.F.R. § 1.132 filed 3/22/96 (Paper No. 8) is insufficient to overcome the rejection of claims 1-10, and 13 based upon nonenablement as set forth in the last Office action for the reasons set forth above (i.e. Applicants have failed to limit the claims to the deposited mutants). Beyond the reasons set forth above the Shigella mutants deposited do not provide sufficient guidance to practice the invention since applicants have failed to provide a deposit of SC500, SC502, SC503, and SC504. For instance, SC502 and SC503 appear to be necessary to make a Shigella strain which has lost the ability to invade cells as encompassed in the claimed invention (i.e see Example 3; and applicants' response page 6 of Paper No. 7). For the reasons set forth above and in the last Office Action said rejection is maintained.

9. The prior rejection of claims 1-10, and 13 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

12. The prior rejection of claim 13 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Sekizaki et al. (Infection and Immunity 55(9):2208-2214 1987) is maintained.

Sekizaki et al. disclose Shigella mutants which lost the ability to produce high levels of Shiga toxin (see abstract and page 2212). Sekizaki et al. does not characterize the Shigella mutant as claimed. Nevertheless it is reasonable for one of ordinary skill in the art to conclude the mutant strain as claimed is the same or an obvious or analogous variant as the

mutant strains as set forth by Sekizaki et al. since they have the same functional properties (i.e. Shigella mutant which has lost the ability to produce high levels of Shiga toxin).

Applicants are advised that since the Office does not have the facilities for examining and comparing applicant's product with the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Applicants essentially argue the mutant *Shigella* strain as set forth by Sekizaki et al. has not lost the ability to produce toxins in contrast to the SC501. Applicants arguments are not persuasive. Sekizaki et al. disclose Shigella mutants which lost the ability to produce high levels of Shiga toxin (see abstract and page 2212). It is reasonable to conclude the mutant strain as claimed is the same or an obvious or analogous variant as the mutant strains as set forth by Sekizaki et al. since they have the same functional properties (i.e. Shigella mutant which has lost the ability to produce high levels of Shiga toxin). While it may be true that the method of obtaining the two is distinct, as asserted by applicants the production of a product by a particular process does not impart novelty or unobviousness to a product when the product is taught by the prior art. This is particularly true when the properties of the product are not changed by the process in an unexpected manner.

See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972).

Therefore even if a particular process used to prepare a product is novel and unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art.

See In re King, 107 F. 2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); In re Merz, 97 F. 2d 599, 601, 38 USPQ 143-45 (CCPA 1938); In re Bergy, 563 F. 2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) vacated 438 US 902 (1978); and United States v. Ciba-Geigy Corp, 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

Furthermore in response to Applicant's argument that Sekizaki et al. does not include certain features of Applicant's invention, the limitations on which the Applicant relies (i.e., the method of obtaining the product, the particular Shigella strain noted (i.e. SC501 *Shigella*)) is not stated in the claim. Therefore, it is irrelevant whether the reference includes those features or not.

13. The prior rejection of claims 1-10 under 35 U.S.C. § 103 as being unpatentable over Mills et al. in view of Sekizaki et al., Nassif et al., Makino et al., and Ozenberger et al. is maintained.

Mills et al. teach the attenuation of Shigella can be achieved by loss of, or deletion of genes from the large virulence plasmid that specifies bacterial invasion as well as site directed inactivation of the toxin gene. Mills et al. teaches the potential for reversion to virulence represent possible problems (see last paragraph).

Mills et al. and Sekizaki et al. both teach of methods of replacing the Shigella toxin gene with a mutant allele. Sekizaki et al. suggests that toxin production is hazardous.

Ozenberger et al. teaches of using methods of insertion and deletions of the siderophore gene enterobactin to impair the ability to grow.

Nassif et al. teaches that Shigella flexerni mutant which no longer produces the siderophore aerobactin displays altered extracellular growth capacity. Nassif et al. teaches it would not be expected to provide sufficient attenuation, but it would certainly be considered additional security (see last paragraph).

Makino et al. disclose a region on the large virulence plasmid of Shigella (the virG gene) is required for cell-cell spread and is involved in the pathogenesis of Shigella. Makino et al. teaches that the mutant may be a plausible candidate for a vaccine (see page 554, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate into the method of attenuating Shigella by inactivating genes required for bacterial invasion and/or Shigella toxin as described by Mills and Sekizaki et al., inactivation of the gene required for aerobactin as taught by Nassif et al. and the inactivation of the gene required for cell-cell spread (virG) as taught by Makino et al. using methods of allelic exchange and/or deletion mutagenesis as taught by Mills, Sekizaki et al, or Ozenberger et al. for the expected benefit of developing a vaccine since as described by Sekizaki et al. toxin production is a hazard in a vaccine, virG and aerobactin are useful in a vaccine (see Nassif et al. and Makino et al.) and aerobactin mutant provides additional security for sufficient attenuation in a vaccine (see Mills et al. and Nassif et al.).

Applicants' argue that there needs to be motivation to combine the references. It is the Examiner's position that there is motivation to combine. VirG and aerobactin are useful in a vaccine (see Nassif et al. and Makino et al.), aerobactin mutant provides additional security for sufficient attenuation in a vaccine (see Mills et al. and Nassif et al.), Mills et al.

teaches the potential for reversion to virulence represent possible problems (see last paragraph).

Applicant appear to argue that Mills does not characterize the location of deletions from the large virulence plasmid. While this may be true it is clear that one of ordinary skill in the art would be able to use transposon mutagenesis or loss of the plasmid of the development of mutants as described by Mills et al. For the reasons stated above and in the last Office Action said rejection is maintained.

14. The prior provisional rejection of Claim 13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 39 of copending application Serial No. 08/118,100 is maintained.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to *Shigella* mutant which has an inactivated Shiga toxin gene (Shiga-toxin A).

Applicants request to hold this rejection in abeyance until allowable subject matter has been indicated. Applicants argument is noted. However, since no allowable subject matter has been indicated the prior provisional rejection of claim 13 under the judicially created doctrine of obviousness-type double patenting is maintained as set forth in the last Office Action.

NEW GROUNDS OF REJECTION

15. Claims 1-10 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36, 37, 38, and 40 of copending application Serial No. 08/118,100. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to *Shigella* mutant which has an inactivated gene encoding Shiga toxin, aerobactin, enterocholin.

inactivated gene encoding the Shiga toxin, aerobactin, enterocholin, the spread of *Shigella* within cells (i.e. *icsA*).

16. Any inquiry concerning this communication should be directed to Dr. Anthony C. Caputa, whose telephone number is 703-308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is 703-308-0196.

Papers related to this application may be submitted to Group 1806 by facsimile transmission. Papers should be faxed to Group 1806 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-308-4242.

Anthony C. Caputa, Ph.D.

June 22, 1996

A. C. CAPUTA
PRIMARY EXAMINER
GROUP 1800